Irritable Bowel Syndrome

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
alosetron (Lotronex®)[1]	Prometheus	Treatment of severe, diarrhea-predominant irritable bowel syndrome (IBS-D) in women who have failed conventional therapy
linaclotide (Linzess®)[2]	Forest	Treatment of chronic idiopathic constipation (CIC) Treatment of irritable bowel syndrome with constipation (IBS-C)
lubiprostone (Amitiza®)[3]	Takeda	Treatment of chronic idiopathic constipation (CIC) Treatment of irritable bowel syndrome with constipation (IBS-C) in females Treatment of opioid-induced constipation in adults with chronic, non-cancer pain

Effectiveness of lubiprostone in the treatment of opioid-induced constipation in patients taking diphenylheptane opioids (e.g., methadone) has not been established.

OVERVIEW[4,5,6,7]

The American Gastroenterological Association (AGA) classifies constipation as a syndrome that is defined by bowel symptoms specific to the difficult passage of stool, infrequent passage of stool, abnormal hardness of stool, or a feeling of incomplete evacuation after a bowel movement. Though constipation can occur secondary to another disease (e.g., Parkinson's disease, spinal cord injury), idiopathic constipation, occurs independent of any other underlying disorder. Chronic idiopathic constipation (CIC) is diagnosed if there are less than three spontaneous bowel movements (SBMs) per week and at least one of the previously mentioned symptoms occurring with at least one out of four stools for at least 12 weeks out of the preceding 12 months.

Irritable bowel syndrome (IBS) is a functional bowel disorder which can be chronic, relapsing and often life long. IBS occurs in up to 15 percent of the population and is up to two and a half times more common in women than men. IBS is characterized by symptoms of abdominal pain or discomfort associated with abnormal stool frequency, abnormal stool form, abnormal stool passage, and/or bloating or abdominal distension, which may or may not be relieved by defecation. Patients present with a combination of symptoms that are typically constipation predominant (IBS-C), diarrhea predominant (IBS-D), and/or alternating between both "mixed" (IBS-M). Patients with IBS experience significant negative impact on their quality of life due to adverse symptoms. Causes of IBS have not been fully identified, but could potentially include gut hypersensitivity, disturbed colonic motility, post-infective bowel dysfunction, or a defective anti-nociceptive system. There may also be contributing factors (stress, food intolerance, abnormal intestinal flora) which can hinder the effectiveness of treatment if left unresolved.

Symptoms of IBS are common to other gastrointestinal (GI) disorders and it is important to assess the presence of warning signs (fever, unintended weight loss, blood in stool, anemia, abnormal physical finding or blood studies, family history of inflammatory bowel disease or cancer), which might be indicative of a more serious condition. Diagnosis of IBS usually occurs in the presence of symptoms while excluding organ disease or other GI disorders. IBS can also present with non-colonic features (functional urinary and gynecologic problems, gallbladder and stomach symptoms, back pain, migraine, and depression) which can lead to inappropriate patient referrals.

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IBS is a chronic condition without a cure. Therefore, treatment of IBS is based on management of the patient's symptoms and may require a combination of modalities to achieve relief. In 2008, the National Institutes of Health and Clinical Excellence (NICE) released clinical practice guidelines for IBS in adults. The AGA also has recommendations presented in their 2002 medical position statement on IBS, and the treatment guidance presented by the AGA and NICE are consistent in their approach. These guidelines recommend diet and lifestyle modifications, patient education and self help, pharmacological agents, behavioral and psychological therapies, and complimentary and alternative therapies. Patients with mild symptoms often respond to dietary changes, such as increasing fiber intake and reducing exposure to intolerant foods, while pharmacologic intervention are typically reserved for patients with moderate to severe symptoms. As needed usage of antispasmodics (e.g. dicyclomine, hyoscyamine) and antidiarrheals (e.g., loperamide, atropine/diphenoxylate) can be used to treat mild to moderate symptoms of IBS-D, while more severe symptoms may necessitate scheduled dosing. Laxatives (e.g. docusate, bisacodyl, sennosides, polyethylene glycol, magnesium hydroxide, lactulose) can be used to treat mild to moderate symptoms of IBS-C, while linaclotide (Linzess) and lubiprostone (Amitiza) are reserved for patients with moderate to severe symptoms. Other considerations can include rifaximin for moderate to severe IBS-D and tricyclic antidepressants for moderate to severe IBS-C and IBS-D. Although the aforementioned medications have historically been used, only linaclotide and lubiprostone have achieved FDA approval for the indication of IBS-C. The NICE guidelines expressly state that no single drug will alleviate the multiple symptoms experienced with IBS and suggest management be focused on the predominant symptom which may require concomitant use of medications and other therapeutic interventions. Newly released agents acting at the 5-HT receptor may help painful symptoms, and must be used based on whether the stool habit is primarily diarrhea (e.g., alosetron) or constipation. No data exist as to the role in mixed or alternating IBS, and recommendations as to their use as first or second line treatments need to be determined based on issues of efficacy, safety, and cost. Alosetron was voluntarily withdrawn from the US market in 2000 due to ischemic colitis and serious complications of severe constipation. In 2002, it returned to market but with tight restrictions.

PHARMACOLOGY[8,9,10]

Alosetron (Lotronex) is a selective serotonin 5-HT_3 receptor antagonist. The 5-HT_3 receptors are ligand-gated cation channels that are located extensively throughout the GI tract, as well as, other peripheral and central sites. When activated, these channels regulate processes that cause many of the symptoms of IBS-D including visceral pain, colonic transit, and gastrointestinal secretions. The 5-HT_3 receptor antagonists inhibit the activation of these channels resulting in modulation of the GI tract.

Linaclotide (Linzess) is a guanylate cyclase-C (GC-C) agonist. Both linaclotide and its active metabolite bind to GC-C and act locally on the luminal surface of the intestinal epithelium. Activation of GC-C results in an increase in both intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP). Elevation in intracellular cGMP stimulates secretion of chloride and bicarbonate into the intestinal lumen, mainly through activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel. This results in increased intestinal fluid and accelerated transit. In animal models, linaclotide has been shown to both accelerate GI transit and reduce intestinal pain. The linaclotide induced reduction in visceral pain in animals is thought to be mediated by increased extracellular cGMP, which was shown to decrease the activity of pain-sensing nerves.

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Lubiprostone (Amitiza) activates ClC-2 chloride channels which produces a chloride-rich intestinal fluid secretion without altering serum electrolyte concentrations. The majority of the beneficial biological activity of lubiprostone and its metabolites are observed only on the apical (luminal) portion of the gastrointestinal epithelium. By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine, thereby facilitating the passage of stool and alleviating symptoms associated with chronic idiopathic constipation.

PHARMACOKINETICS

Drug	Bioavailability (%)	Half-Life	Metabolism	Excretion
alosetron (Lotronex®)[11]	50 – 60	1.5 hr	Predominately metabolized by cytochrome P450 enzymes 2C9, 3A4, and 1A2	Urine (74%) Feces (11%)
linaclotide (Linzess)[12]	n/a*	n/a*	Proteolytically degraded in the lumen to smaller peptides and naturally occurring amino acids	Feces
lubiprostone (Amitiza)[13]	n/a*	n/a*	Rapidly and extensively metabolized by carbonyl reductase mediated oxidation and reduction	Feces

*Standard pharmacokinetic parameters cannot be calculated due to immeasurable plasma concentrations following therapeutic oral doses.

CONTRAINDICATIONS/WARNINGS[14,15, 16]

Alosetron (Lotronex) is contraindicated in patients with a history of ischemic colitis or serious GI disease, such as GI obstruction, perforation, stricture, toxic megacolon, or GI adhesions. Alosetron is contraindicated in patients currently experiencing or with a history of thrombophlebitis, severe hepatic impairment, impaired intestinal circulation, diverticulitis, Crohn's disease, ischemic or ulcerative colitis and should not be used in patients with constipation.

Both linaclotide (Linzess) and lubiprostone (Amitiza) are contraindicated in patients with known or suspected mechanical GI obstruction.

Linaclotide carries a boxed warning against its use in children up to six years of age and should not be used in children up to 17 years of age.

Allergic-type reactions have been reported with the use of lubiprostone.

DRUG INTERACTIONS[17,18, 19]

Based on data from *in vivo* studies, alosetron is predominately metabolized by cytochrome P450 1A2, with minor contributions from CYP3A4 and CYP2C9. Inducers or inhibitors of these enzymes, such as fluvoxamine or ketoconazole, may alter the metabolism and clearance of alosetron (Lotronex).

No drug-drug interaction studies have been conducted for linaclotide (Linzess) or lubiprostone (Amitiza), however, there is a low potential for serious or significant drug interactions due to very low systemic bioavailability. Neither linaclotide nor lubiprostone is a substrate, inhibitor, or inducer of any cytochrome P450 metabolic pathway. Drug interactions mediated by protein binding are not anticipated with linaclotide or lubiprostone. Pharmacodynamic drug interactions can be anticipated

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with agents that oppose the action of drugs to treat constipation. This includes medications that decrease GI motility or have anticholinergic effects.

ADVERSE EFFECTS

Drug	Constipation	Diarrhea	Nausea	Abdominal Pain	Flatulence	Abdominal Distension	Viral Gastroenteritis	Headache	Dyspnea
alosetron (Lotronex)[20] n=8,328	29 (6)	nr	6 (5)	7 (4)	nr	2 (1)	nr	nr	nr
linaclotide (Linzess)[21] n=807	nr	20 (3)	nr	7 (5)	4 (2)	2 (1)	3 (1)	4 (3)	nr
lubiprostone (Amitiza)[22] n=1,113	nr	12 (<1)	29 (3)	8 (3)	6 (2)	6 (2)	nr	11 (5)	2 (0)

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for placebo groups are indicated in parentheses. nr = not reported.

Constipation is a dose-related adverse effect of alosetron (Lotronex) and the most frequently reported adverse effect in clinical trials. Constipation associated with alosetron is generally reported as mild to moderate in intensity, transient in nature, and resolved either spontaneously or upon discontinuation of the drug. There have been reports of serious complications of constipation in clinical trials and postmarketing data including obstruction, ileus, impaction, toxic megacolon, and secondary bowel ischemia. Due to the risk associated with using alosetron, prescribers must be enrolled in the Prescribing Program for Lotronex. Patients who are elderly, debilitated, or taking other medications that decrease GI motility may be at greater risk for complications of constipation. Alosetron should be discontinued immediately in any patient experiencing constipation.

Severe diarrhea was reported in approximately two percent of the patients taking linaclotide (Linzess) and lubiprostone (Amitiza). If severe diarrhea occurs, the patient should be instructed to contact their provider and dosing of the drug may need to be interrupted or suspended.

The most common adverse effect associated with lubiprostone is nausea. The incidence of nausea increases in a dose-dependant manner with the highest percentage being reported in patients receiving 24 mcg twice daily dosing. It is recommended that lubiprostone be given with food and water which was shown to decrease reported nausea.

Dyspnea with lubiprostone has been reported and usually occurs within 30 to 60 minutes of taking the first dose. Described as a sensation of chest tightness and difficulty taking in a breath, these symptoms generally resolve within three hours after taking the dose but recurrence has been frequently reported with subsequent doses.

SPECIAL POPULATIONS[23,24, 25]

Pediatrics

Safety and effectiveness have not been established in pediatric patients for alosetron (Lotronex), linaclotide (Linzess) or lubiprostone (Amitiza).

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In nonclinical animal studies, deaths occurred within 24 hours following one to two daily oral doses of linaclotide in juvenile mice equivalent to human pediatric patients two years of age. Linaclotide did not cause death in older juvenile mice equivalent to human pediatric patients twelve through 17 years of age. However, due to deaths in the younger juvenile mice and the lack of clinical safety and efficacy data, linaclotide is contraindicated in pediatric patients up to six years of age and should be avoided in patients six years through 17 years of age.

Pregnancy

Alosetron is classified as FDA pregnancy risk category B.

Linaclotide and lubiprostone are classified as FDA pregnancy risk category C.

Renal Impairment

No dose adjustment is necessary based on renal function for alosetron, linaclotide or lubiprostone.

Hepatic Impairment

Alosetron is contraindicated in patients with severe hepatic impairment and should be used cautiously in patients with mild to moderate hepatic impairment.

No dose adjustment is needed based on hepatic function for linaclotide.

For the treatment of CIC with lubiprostone, the recommended dose for patients with moderately impaired hepatic function (Child-Pugh Class B) is 16 mg twice daily. For patients with severely impaired hepatic function (Child-Pugh Class C), the recommended dose is 8 mcg twice daily. If tolerated, the dose can be escalated to full dosing with appropriate monitoring of patient response.

For the treatment of IBS-C, there is no dose adjustment of lubiprostone needed for patients with moderately impaired hepatic function (Child-Pugh Class B). For patients with severely impaired hepatic function (Child-Pugh Class C), the recommended dose is 8 mcg once daily. If tolerated, the dose can be escalated to full dosing with appropriate monitoring of patient response.

DOSAGES[26,27, 28]

Drug	Severe Diarrhea-Predominant Irritable Bowel Syndrome	Availability
alosetron (Lotronex)	0.5 mg twice a day, may increase to 1 mg twice a day if well tolerated (discontinue if 4 weeks' treatment at this dose does not lead to adequate symptom control)	0.5 mg and 1 mg tablets

Drug	Chronic Idiopathic Constipation	Irritable Bowel Syndrome with Constipation	Availability
linaclotide (Linzess)	145 mcg once daily*	290 mcg once daily	145 mcg and 290 mcg capsules
lubiprostone (Amitiza)	Females: 24 mcg twice daily† Males: 24 mcg twice daily†	Females: 8 mcg twice daily Males: n/a**	8 mcg and 24 mcg capsules

*In CIC, the 290 mcg linaclotide dose has not been shown to be more effective than the 145 mcg dose.

**Safety and efficacy has not been established for the use of lubiprostone in males for IBS-C

†Same dose used for treatment of opioid-induced constipation in adults with chronic, non-cancer pain

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CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Due to the paucity of comparative trials, placebo-controlled studies are included.

alosetron (Lotronex) versus placebo

The efficacy and tolerability of alosetron in non-constipated female patients with IBS were evaluated in a double-blind, randomized, placebo-controlled trial. Patients received either 1 mg of alosetron (n=309) or placebo (n=317) twice daily for 12 weeks, followed by a four-week post-treatment period.[29] Adequate relief of IBS pain and discomfort was the primary end point. Secondary end points included improvements in urgency, stool frequency, stool consistency, incomplete evacuation, and bloating. A total of 71 percent of patients were classified as having IBS-D. Forty-three percent of alosetron-treated patients with IBS-D reported adequate relief for all three months compared with 26 percent of placebo-treated patients ($p<0.001$; 95% confidence interval, 8.0-25.4). Improvement with alosetron compared with placebo was observed by the end of the fourth week of treatment and persisted throughout the remainder of treatment. Alosetron significantly decreased urgency and stool frequency and caused firmer stools within one week of starting therapy. Effects were sustained throughout treatment and symptoms returned following treatment cessation. No significant improvement in the percentage of days with sense of incomplete evacuation or bloating was observed compared with placebo during the first month of treatment. Constipation was the most commonly reported adverse event.

A randomized, double-blind, placebo-controlled study assessed long-term safety and efficacy of alosetron in women with severe, chronic IBS-D and in a subset having more frequent urgency (e.g. bowel urgency at least 10 of 14 days during screening).[30] Patients received either alosetron 1 mg (n=351) or placebo (n=363) twice daily during a 48-week period. The primary endpoint was the 48-week average rate of adequate relief of IBS pain and discomfort. Secondary endpoints included 48-week average satisfactory control rates of urgency, stool frequency, stool consistency, and bloating. Other efficacy endpoints were average monthly adequate relief and urgency control rates and impact of provided rescue medication. Alosetron-treated patients had significantly greater 48-week average adequate relief ($p=0.01$) and urgency control ($p<0.001$) rates compared with placebo. Results in subjects with more frequent urgency were stronger than those in the overall population ($p=0.005$).

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Alosetron-treated patients had significantly greater adequate relief than placebo-treated patients ($p< 0.05$) in nine of 12 months and significantly greater urgency control ($p<0.001$) in all months. Adequate relief and urgency control were maintained throughout the treatment. Adverse events and serious adverse events were similar between treatment groups, except for constipation. Neither ischemic colitis nor serious events related to bowel motor dysfunction was reported.

A randomized, placebo-controlled trial evaluated the effect of alosetron on bowel urgency and IBS global improvement in IBS-D.[31] Women with a lack of satisfactory bowel urgency control at least 50 percent of the time during screening were randomized to receive alosetron 1 mg (n=246) or placebo (n=246) twice daily. The primary end point was the percentage of days with satisfactory control of bowel urgency. The response rate for the IBS global improvement scale (GIS) was a secondary end point. GIS responders were patients who recorded either moderate or substantial improvement in IBS symptoms relative to the way they felt before entering the study. Other end points included improvement in stool frequency, stool consistency, and percentage of days with incomplete evacuation. Further analyses were performed on a subset of patients who had at least 10 of 14 days during screening (≥71 percent of days) with a lack of satisfactory control of bowel urgency. Patients had severe chronic IBS symptoms, and 89 percent of patients had IBS-D. Alosetron resulted in a greater percentage of days with satisfactory control of urgency compared with placebo (69 percent versus 56 percent, respectively, $p<0.001$). Greater percentages of alosetron-treated patients were GIS responders at 4, 8, and 12 weeks compared with placebo (59 percent versus 41 percent, 63 percent versus 41 percent, and 68 percent versus 46 percent, respectively, $p<0.001$). Patients with more frequent urgency had similar results. Constipation occurred in 28 percent and nine percent of subjects in the alosetron and placebo-treated groups, respectively. No cases of ischemic colitis were reported.

linaclotide (Linzess) versus placebo

The efficacy of linaclotide for the management of symptoms of IBS-C was established in two double-blind, placebo-controlled, randomized, multicenter trials in adult patients (Trials 1 and 2).[32,33,34] A total of 800 patients in trial 1 and 804 patients in trial 2 received treatment with linaclotide 290 mcg or placebo once daily. The trial designs were the same through the first 12 weeks. Trial 1 included a four week randomized withdrawal period after the initial 12 weeks and Trial 2 continued for 14 additional weeks (total of 26 weeks) of double-blind treatment. During the trials, patients were allowed to continue stable doses of bulk laxatives or stool softeners but were not allowed to take laxatives, bismuth, prokinetic agents, or other drugs to treat IBS-C or chronic constipation. There were four primary endpoints for these trials. Patients were considered an abdominal pain responder if they experienced at least a 30 percent reduction from baseline in mean abdominal pain. Patients were considered a complete spontaneous bowel movement (CSBM) weekly responder if they had at least three CSBMs and an increase of at least one CSBM from baseline all in the same week. The primary endpoint of CSBM weekly responders for at least nine out of the 12 weeks of treatment with linaclotide versus placebo was 19.5 percent versus 16.3 percent (treatment difference 3.2 percent; 95% CI, 8.6 to 17.7) in trial 1 and 18 percent versus five percent (treatment difference 13 percent; 95% CI, 8.7 to 17.3) in trial 2. The primary endpoint of abdominal pain responder for at least nine out of 12 weeks of treatment with linaclotide versus placebo was 34.3 percent versus 27.1 percent (treatment difference 7.2 percent; 95% CI, 0.9 to 13.6) in trial 1 and 38.9 percent versus 19.6 percent (treatment difference 19.3 percent; 95% CI, 13.2 to 25.4) in trial 2. The primary endpoint of combined CSBM weekly responder and abdominal pain responder for nine out of 12 weeks of treatment with linaclotide versus placebo was 12.1 percent versus 5.1 percent (treatment difference seven percent; 95% CI, 3.2

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to 10.9) in trial 1 and 12.7 percent versus three percent (treatment difference 9.7 percent; 95% CI, 6.1 to 13.4) in trial 2. The primary endpoint of abdominal pain responders with an increase of at least one CSBM per week for at least six out of the 12 weeks of treatment with linaclotide versus placebo was 33.6 percent versus 21 percent (treatment difference 12.6 percent; 95% CI, 6.5 to 18.7) in trial 1 and 33.7 percent versus 13.9 percent (treatment difference 19.8 percent; 95% CI, 14 to 25.5) in trial 2. During the four week randomized withdrawal period in trial 1, patients who received linaclotide during the 12-week treatment period were re-randomized to receive placebo or continue treatment on linaclotide 290 mcg. In linaclotide-treated patients re-randomized to placebo, CSBM frequency and abdominal-pain severity returned toward baseline within one week and did not result in worsening compared to baseline. Patients who continued on linaclotide maintained their response to therapy over the additional four weeks. Patients on placebo who were allocated to linaclotide had an increase in CSBM frequency and abdominal pain levels that were similar to the levels observed in patients taking linaclotide during the treatment period. The percentage of adverse reactions reported from both trials in at least two percent of the study patients and at an incidence greater than placebo included diarrhea (linaclotide 20 versus placebo three), abdominal pain (seven versus five), flatulence (four versus two), abdominal distension (two versus one), viral gastroenteritis (three versus one), and headache (four versus three).

The efficacy of linaclotide for the management of symptoms of CIC was established in two double-blind, placebo-controlled, randomized, multicenter clinical trials in adult patients (Trials 3 and 4).[35, 36] A total of 642 patients in trial 3 and 630 patients in trial 4 received treatment with linaclotide 145 mcg, 290 mcg, or placebo once daily. All patients included in the trial met criteria for functional constipation and were excluded if they met criteria for IBS-C or had fecal compaction. The trial designs were identical through the first 12 weeks. Trial 3 also included an additional four week randomized withdrawal period. During the trials, patients were allowed to continue stable doses of bulk laxatives or stool softeners but were not allowed to take laxatives, bismuth, prokinetic agents, or other drugs to treat chronic constipation. The primary endpoint was defined as a patient who had at least three CSBMs and an increase of at least one CSBM from baseline in a given week for at least nine out of the 12 week period. In trial 3, the primary endpoint was achieved in 20.3 percent of patients taking linaclotide versus 3.3 percent of patients taking placebo (treatment difference 16.9 percent; 95% CI, 11 to 22.8). In trial 4, the primary endpoint was achieved in 15.5 percent of patients taking linaclotide verses 5.6 percent of patients taking placebo (treatment difference 9.9 percent; 95% CI, 4.2 to 15.7). Linaclotide 290 mcg did not consistently offer additional clinically meaningful treatment benefit over placebo than that observed with the 145 mcg dose. During the four week randomized withdrawal period in trial 3, patients who received linaclotide during the 12-week treatment period were re-randomized to receive placebo or continue treatment on the same dose taken during the treatment period. In linaclotide-treated patients re-randomized to placebo, CSBM and spontaneous bowel movement (SBM) frequency returned toward baseline within one week and did not result in worsening compared to baseline. Patients who continued on linaclotide maintained their response to therapy over the additional four weeks. Patients on placebo who were allocated to linaclotide had an increase in CSBM and SBM frequency similar to the levels observed in patients taking linaclotide during the treatment period. The percentage of adverse reactions reported from both trials in at least two percent of the study patients and at an incidence greater than placebo included diarrhea (linaclotide 16 versus placebo five), abdominal pain (seven versus six), flatulence (six versus five), abdominal distension (three versus two), upper respiratory tract infections (five versus four), and sinusitis (three versus two).

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lubiprostone (Amitiza) versus placebo

In two double-blinded, placebo-controlled studies of identical design, lubiprostone was studied in patients with CIC.[37] A total of 479 were randomized and received Amitiza 24 mcg twice daily or placebo twice daily for four weeks. The primary endpoint of the studies was spontaneous bowel movement (SBM) frequency. The change in SBMs frequency rate from baseline to week one for lubiprostone versus placebo was 4.3 versus 1.9 in study 1 and 4.5 versus 2.5 for placebo. The change in SBM frequency rate from baseline to week four for lubiprostone versus placebo was 3.9 versus 1.3 in study 1 and 4.1 versus 1.9 in study 2. The percentage of adverse effects occurring in at least two percent of lubiprostone-treated patients and that occurred more frequently than placebo include nausea (lubiprostone 29 versus placebo three), diarrhea (12 versus one), abdominal pain (eight versus three), headache (11 versus five), abdominal distension (six versus two), flatulence (six versus two), vomiting (three versus zero), dizziness (three versus less than one), loose stools (three versus zero), edema (three versus less than one), abdominal discomfort (two versus less than one), dyspepsia (two versus less than one), and fatigue (two versus less than one).

Two double-blinded, placebo-controlled studies of similar design were conducted studying lubiprostone in patients with IBS-C.[38] A total of 1,154 patients were randomized and received lubiprostone 8 mcg twice daily or placebo twice daily for 12 weeks. The primary efficacy endpoint was assessed weekly utilizing the patients' response to a questionnaire. The percentage of patients in study 1 qualifying as an "overall responder" was 13.8 percent in the group receiving lubiprostone compared to 7.8 percent of patients receiving placebo. In Study 2, 12.1 percent of patients in the lubiprostone group were "overall responders" versus 5.7 percent of patients in the placebo group. In both studies, the treatment differences between the placebo and lubiprostone groups were statistically significant. There were not a sufficient number of men included in the studies to determine whether men respond differently to lubiprostone from women. The percentage of adverse effects occurring in at least two percent of lubiprostone-treated patients and that occurred more frequently than placebo include nausea (lubiprostone eight versus placebo four), diarrhea (seven versus four), abdominal pain (five versus five), headache (11 versus five), and abdominal distension (three versus two).

Three randomized, double-blind, placebo-controlled trials compared lubiprostone 24 mcg twice daily with placebo for 12 weeks in about 1,300 patients with chronic noncancer pain and opioid-induced constipation (defined as greater than three spontaneous bowel movements [SBMs] per week).[39] In one study in patients taking full-agonist opioids other than methadone, the primary efficacy endpoint of overall response (≥3 SBMs per week for at least 9 of the 12 weeks, and at least 1 more SBM per week than at baseline in every week for which data was available) was achieved in 27.1 percent of patients taking lubiprostone versus 18.9 percent of placebo (treatment difference=8.2 percent; p=0.03). The other two studies did not exclude patients taking methadone; treatment with lubiprostone, compared to placebo, resulted in a significantly greater improvement from baseline in weekly SBM frequency at week 8 (the primary endpoint) in one study (3.3 versus 2.4, p=0.004) but not the other (2.7 versus 2.5, p=0.76); overall response rates in the two studies were 24.3 percent and 15.3 percent for lubiprostone versus 15.4 percent and 13 percent for placebo.

SUMMARY

Treatment for irritable bowel syndrome (IBS) focuses on management of symptoms and pharmacologic options should be considered as part of a multifocal approach to achieve relief. Alosetron is limited to

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women with severe IBS-D who have not responded adequately to conventional therapy and have shown greater improvement of symptoms associated with IBS-D versus placebo. Alosetron should only be prescribed by enrollees of the Prometheus Prescribing Program for Lotronex due to the possible risk of severe complications of constipation and ischemic colitis. Linaclotide (Linzess) and lubiprostone (Amitiza) are indicated for the treatment of chronic idiopathic constipation (CIC) and IBS with constipation (IBS-C), though lubiprostone is not indicated for use in IBS-C for men. Lubiprostone is also approved for the treatment of opioid-induced constipation in adults with chronic, non-cancer pain. Despite a lack of comparative data between linaclotide and lubiprostone, both have been shown to be more effective than placebo in alleviating the symptoms associated with IBS-C, however it is important that these medications not be used in patients with gastrointestinal (GI) obstruction. Diarrhea can occur with the use of both agents and, if severe, may require dosing interruption. The use of lubiprostone has been associated with hypersensitivity reactions and nausea, which have not been reported with linaclotide. Furthermore, linaclotide does not require dose adjustment for patients with hepatic impairment and is dosed once daily versus twice daily administration with lubiprostone. The role of these agents in the treatment of IBS-C, IBS-D, and CIC continues to be determined given lack of comparative data and controlled data with long-term safety, remains to be established.

REFERENCES

1 Lotronex [package insert]. San Diego, CA; Prometheus Laboratories, Inc; September 2010.
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